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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Richard J. Wurtman et al GROUP 125

SER. NO. : 159,549 EXAMINER: Caccipaglia

FILED : June 16, 1980

FOR : METHOD AND COMPOSITION FOR UTILIZING d-FENFLURAMINE FOR MODIFYING FEEDING BEHAVIOR

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

RESPONSE

Claims 5 and 6 have been rejected under 35 USC 103 over references S, T and V in view of Beregi et al. It is the Examiner's position that since Beregi et al teaches that the d-isomer is more active as an anoretic agent, to further demonstrate that the d-isomer additionally is more active than the racemate for the same purpose taught in the primary references is seen to involve no patentably significant unexpected result.

It is believed that the Examiner's conclusion based upon Beregi et al is inappropriate since there is no general correlation between the activity of a general anorexic agent and the activity of such an agent in selectively suppressing carbohydrate intake (i.e., when animals or humans have a trace of several foods, with different proportions of carbohydrate and protein at a particular time). L-fenfluramine is more effective biologically in some systems and equally effective in other systems that have been shown to be related to food consumption. For example:

a. L-fenfluramine but not d-fenfluramine is an agonist for dopamine receptors. (Consolo et al, J. Pharm. Pharmacol., vol. 31, p. 706, 1979; Consolo et al, J. Pharm. Pharmacol., vol. 32, pp. 201-203, 1980). This action could conceivable be in-

volved in the general anorexic effect of the l-fenfluramine. This is because dopamine receptors preferably underlie amphetamine's anorexic effects, i.e. amphetamine releases the dopamine which then reacts on receptors while l-fenfluramine acts directly on these receptors. D-fenfluramine acts neither indirectly nor directly on the dopamine receptors.

b. L-fenfluramine is slightly more potent that d-fenfluramine in displacing serotonin from the protein to which it is bound, prior to being released from nerve terminals in the brain. The IC 50 (in micromolarity) for the l-isomer is 0.22, while that for the d-isomer is 0.27. Since the selective suppression of carbohydrate intake derives from the increase in serotoninergic transmission produced by the drug, these observations would lead one skilled in the art that the isomers would have approximately equal efficacy in suppressing carbohydrate intake. As shown in applicants' specification, this is not the case since the d-isomer is far more active in suppressing carbohydrate intake.

c. Applicants, in preliminary studies on human subjects with carbohydrate cravings, have found that a major suppression of excessive carbohydrate intake can be obtained using doses of dl-fenfluramine well below those needed clinically to produce general anorexia. This affirms that a <u>different mechanism</u> from that causing general anorexia underlies the carbohydrate-suppressant effect.

d. d-norfenfluramine, i.e. metabolite of d-fenfluramine is even more potent as a general anorexant but has no specific effect on carbohydrate intake.

It is submitted that the facts regarding d-fenfluramine, l-fenfluramine and the racemic mixtures set forth above establish that the person skilled in the art could not have predicted the relative activities of the two isomers on the suppression of carbohydrate intake based upon the relative activities of the two isomers on anorexic activity. Accordingly, it is submitted that the person skilled in the art would find it unexpected that the d-isomer is more active in suppressing carbohydrate craving as compared to the l-isomer. In view of this, it is submitted that applicants' claims define patentable subject matter and an early notice of allowance to that effect is respectfully requested.

Respectfully submitted,

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Signature Date: 5/6/81

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